UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,423	02/10/2004	Alexander B.H. Bakker	DX0763XB2	9728

28008 7590 11/15/2006

DNAX RESEARCH INC.
LEGAL DEPARTMENT
901 CALIFORNIA AVENUE
PALO ALTO, CA 94304

EXAMINER
O'HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/775,423	BAKKER ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 21-30 are pending in the instant application. Claims 1-20 have been canceled and claims 21-30 have been added as requested by Applicant in the Paper filed January 20, 2004.

Election/Restrictions

2. Applicant's election of Group I in the reply filed on Sept. 5, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's further election with traverse of human MDL-I protein is acknowledged. The traversal is on the ground(s) that the human and mouse MDL-1 possess greater than 130 out of 190 identical amino acid residues and searching both proteins would not be a burden. This is found persuasive and both human and mouse proteins will be examined.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-6 are currently under examination.

Specification

3.0 The disclosure is objected to because of the following informalities:

3.1 37 C.F.R. §1.821(d) states:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section,

> reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The instant specification needs to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. For example, on page 23, line 1, sequences are referred to as Tables and not SEQ ID NO, and on page 15, the human and mouse sequences are not identified by SEQ ID NO. Also, claim 2 refers to MDL-1 protein of Table 3. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Applicants are required to amend the specification and claims to comply with 37 C.F.R. §1.821(d).

3.2 The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: MDL-1 proteins.

Priority

4. Applicant is reminded of the following requirement:

In a continuation or divisional application (other than a continued prosecution application filed under 37 CFR 1.53(d)), the first sentence of the specification or application data sheet (37 CFR 1.76) should include a reference to the prior application(s) from which benefit of priority is claimed, and also the status. See 37 CFR 1.78. This application is a divisional of USSN 10/191,732, now U.S. Patent No. 6,953,843, which should be included in the first sentence.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

6. Claims 1-4 are objected to because of the following informalities: they are drawn to nonelected inventions, which should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7.1 Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides exhibiting identity over at least about 12 amino acids to the mature SEQ ID NO: 12 or 14, wherein the polypeptide may be a "natural" sequence

such as a natural allelic variant. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of

the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.3.2

1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 12 and 14, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7.2 Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using polypeptide comprising the amino acid sequence of SEQ ID NO: 12 or 14, does not reasonably provide enablement for making and using a polypeptide exhibiting identity over a length at least about 12 amino acids to the mature SEQ ID NO: 12 or 14, wherein the polypeptide may be a "natural" sequence such as a natural allelic variant, or polypeptides of unspecified lengths. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification discloses that DAP-12 is an accessory protein that functions in receptor complexes with several different membrane receptors. The specification teaches that many of the receptors important in the activation of leukocytes (including the T cell antigen

receptor, and immunoglobulin and Fc receptors), lack intrinsic signaling properties, but transmit their signals by coupling con-covalently with other membrane proteins that contain ITAM (immunoreceptor tyrosine-based activation) motifs in their cytoplasmic domains, and provides many examples (page 37, lines 23-37). Therefore, associated proteins containing ITAM represent a general strategy in the assembly of activating receptors on leukocytes. The application teaches that the DAP-12 protein of the instant application has an ITAM motif, non-covalently associates with membrane glycoproteins of the killer inhibitory receptor (KIR) family that lack immunoreceptor tyrosine-based inhibitory motifs (ITIM) in their cytoplasmic domains, and KIR2DS2-DAP12 complexes expressed in transfectants result in cellular activation, as demonstrated by tyrosine-phosphorylation of cellular proteins and up-regulation of early activation antigens. Phosphorylated DAP12 peptides also ind ZAP-70 and Syk protein tyrosine kinases, suggesting an activation pathway similar to the T and B cell antigen receptors (page 54). The instant application also demonstrates that DAP-12 is associated with signaling with other receptors (CD94/NKG2C, pages 56-63, Ly49D or Ly49H, pages 66-69). DAP-12 remains localized intracellulary when expressed in cells in the absence of associating partners. The MDL-1 protein of the instant application was identified in cells expressing DAP-12 transformed with an expression library and identifying clones that expressed DAP-12 on the cell surface (pages 69-71), and it was found that MDL-1 appears to be crucial in localization of the DAP-12 to the membrane. The MDL-1 protein has an intracellular domain of 2 residues, a transmembrane region of 23 residues, and a 140 residue extracellular region. The instant specification hypothesizes that the MDL-1 protein associates with the DAP-12 in the membrane complex, and

that disruption of the complex my lead to interesting blocking of function of the DAP-12 receptor complex.

However, because these claims encompass the variants stated above, and only two polypeptides have been disclosed in the instant specification, the mouse and human orthologs, a practitioner can not make a protein comprising an amino acid sequence other than the one disclosed in the instant specification and expect it to have the same functions. Some guidance is provided by the alignment between the human and the mouse protein (Table 3), which shows that there is about 71% conserved amino acid residues between the two species. However, the instant specification does not identify those amino acid residues in the amino acid sequence of SEQ ID NO: 12 or 14 which are essential for their biological activity and structural integrity and those residues which are either expendable or substitutable. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made

in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis before they could even begin to rationally design a functional protein having other than a natural amino acid sequence. The disclosure of two orthologs with a natural amino acid sequence is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass the other variants. Even acknowledging high skill in the molecular biology art, prediction of which variants would have the same activity as MDL-1 is not possible based on the prior art or on the information provided in the specification. Protein function, cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of

growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does not allow predictability in this instance. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences.

The current claim limitations are analogous to those of claim 7 of U.S. Patent Number 4,703,008 which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 U.S.P.Q. 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance, a claim to a nucleic acid encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement. The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few analogs thereof. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For proteins, that means disclosing how to make and use enough sequences to justify the grant of the claims sought. As indicated, the instant specification is even more limited than the '008 patent because it describes only two naturally occurring orthologs and, therefore, provides even less support than the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

For the reasons discussed above, due to the large quantity of experimentation necessary to generate the large number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples and written description directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any specific functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 are indefinite because claims 1 and 2 encompass a mature seuquence of SEQ ID NOS: 12 or 14, but there is no mature sequence identified in the specification.

Claims 2-4 are indefinite because claim 2 encompasses an MDL-1 polypeptide which is a " natural" sequence, and claim 3 recites a "natural allelic variant". It is not clear what is meant by the term "natural" sequence or allelic variant, or how one of ordinary skill in the art would be able to determine if a sequence is "natural" or not by looking at it.

Claim 2 is also indefinite because the polypeptide comprises a charged residue in "***a***" transmembrane domain, which indicates that there is more than one transmembrane domain, but there is only one transmembrane domain in the protein.

Claim 3 is also indefinite because it encompasses a polypeptide which comprises a "plurality of ***said*** lengths".

Claim 3 is also indefinite because it recites that the polypeptide is conjugated to ***another*** chemical moiety, and there is insufficient antecedent basis for this limitation in the claim.

Claim 3 is also indefinite because it encompasses a polypeptide of claim 1 which is a 5-fold or less substitution from natural sequence, and it is not clear what a "***5-fold*** substitution" is.

Claim 3 is also indefinite because it encompasses a polypeptide which is a deletion or insertion variant from a natural sequence, and a deletion or insertion variant could also be a natural sequence.

Claim 4 is indefinite because it depends from claims 1, 2 and 3.

Pertinent Art

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure, Fraser et al., U.S. Patent Application Publication No. 20030022279, which discloses two proteins (SEQ ID NOS: 86 and 88) that are identical to the proteins of SEQ ID NOS: 12 and 14 of the instant application. This is not considered prior art, since the priority date of the instant application preceeds that of McCarthy et al., and is cited as the closest art.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

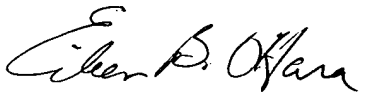
Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to

the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner



EILEEN B. O'HARA
PRIMARY EXAMINER